perceptual learning but also functional ones. A number of theorists have argued that perceptual learning should be considered as independent of more general processes which would not be restricted to stimulus-specific features or locations (for example [10,17]). Relaxing this constraint gives additional support to the alternative view that more general mechanisms such as association formation or categorization can make significant contributions to perceptual learning (for example [18–20]). Similarly, by demonstrating that learning with simple stimuli can be independent of location in the same way as more complex stimuli, Xiao *et al.*'s [8] work raises the possibility that perceptual learning with simple and complex stimuli might rely on at least partially overlapping mechanisms.

In summary, by implicating central, rather than peripheral, mechanisms for perceptual learning with simple visual stimuli the demonstration of complete transfer across retinal locations raises many interesting possibilities. In particular, that there might be more commonalities between perceptual learning with simple and complex stimuli and between general cognitive mechanisms and their perceptual consequences than have previously been supposed.

References

1. Gibson, E.J. (1963). Perceptual learning. Annu. Rev. Psychol. *14*, 29–56.
2. Solomon, G.E.A. (1997). Conceptual change and wine expertise. J. Learn. Sci. *6*, 41–60.
3. Fahle, M. (1997). Specificity of learning curvature, orientation, and vernier discriminations. Vision Res. *37*, 1885–1895.
4. Shiu, L.P., and Pashler, H. (1992). Improvement in line orientation discrimination is retinally local but dependent on cognitive set. Percept. Psychophys. *52*, 582–588.
5. Karni, A., and Sagi, D. (1991). Where practice makes perfect in texture-discrimination - evidence for primary visual-cortex plasticity. Proc. Natl. Acad. Sci. USA *88*, 4966–4970.
6. Mundy, M.E., Honey, R.C., and Dwyer, D.M. (2007). Simultaneous presentation of similar stimuli produces perceptual learning in human picture processing. J. Exp. Psychol. *33*, 124–138.
7. Bruce, V., and Burton, A.M. (2002). Learning new faces. In Perceptual Learning, T. Poggio and M. Fahle, eds. (Cambridge, MA: MIT Press), pp. 317–334.
8. Xiao, L., Zhang, J., Wang, R., Klein, S.A., Levi, D.M., and Yu, C. (2008). Complete transfer of perceptual learning across retinal locations enables by double training. Curr. Biol. *18*, 1922–1926.
9. Fahle, M. (2004). Perceptual learning: A case for early selection. J. Vision *4*, 879–890.
10. Fahle, M. (2002). Introduction. In Perceptual Learning, M. Fahle and T. Poggio, eds. (Cambridge, MA: MIT Press), pp. ix–xx.
11. Dosher, B.A., and Lu, Z.L. (1999). Mechanisms of perceptual learning. Vision Res. *39*, 3197–3221.
12. Mollon, J.D., and Danilova, M.V. (1996). Three remarks on perceptual learning. Spatial Vision *10*, 51–58.
13. Schoups, A., Vogels, R., Qian, N., and Orban, G. (2001). Practising orientation identification improves orientation coding in V1 neurons. Nature *412*, 549–553.
14. Schwartz, S., Maquet, P., and Frith, C. (2002). Neural correlates of perceptual learning: A functional MIR study of visual texture discrimination. Proc. Natl. Acad. Sci. USA *99*, 17137–17142.
15. Mukai, I., Kim, D., Fukunaga, M., Japee, S., Marrett, S., and Ungerleider, L.G. (2007). Activations in visual and attention-related areas predict and correlate with the degree of perceptual learning. J. Neurosci. *27*, 11401–11411.
16. Ahissar, M., and Hochstein, S. (1993). Attentional control of early perceptual-learning. Proc. Natl. Acad. Sci. USA *90*, 5718–5722.
17. Hall, G. (1991). Perceptual and Associative Learning (Oxford: Oxford University Press).
18. McLaren, I.P.L., and Mackintosh, N.J. (2000). An elemental model of associative learning: I. Latent inhibition and perceptual learning. Anim. Learn. Behav. *28*, 211–246.
19. Goldstone, R. (2003). Learning to perceive while perceiving to learn. In Perceptual Organization in Vision: Behavioral and Neural Perspectives, R. Kimchi, M. Behrmann, and C. Olson, eds. (Mahwah, NJ: Lawrence Erlbaum Associates), pp. 233–280.
20. Mundy, M.E., Dwyer, D.M., and Honey, R.C. (2006). Inhibitory associations contribute to perceptual learning in humans. J. Exp. Psychol. *32*, 178–184.

School of Psychology, Cardiff University, Tower Building, Park Place, Cardiff CF10 3AT, UK.
E-mail: DwyerDM@cardiff.ac.uk

DOI: 10.1016/j.cub.2008.10.037

Gene Expression: Dialing Up the Frequency

Cells often respond to external signals by altering their gene expression. The external signaling information is transduced and typically encoded in concentrations of relevant transcription factors. A recent study demonstrates that, by encoding this information in the frequency with which genes 'see' a transcription factor, the expression of hundreds of genes can be modulated in a linearly proportional manner.

Narendra Maheshri

The single input module is a prevalent network motif in genetic regulatory networks that allows cells to respond to external signals through the coordinated regulation of hundreds of genes. This module consists of a transcription factor (TF) that directly regulates the expression of many downstream genes. Typically, external signal information is encoded in the concentration of the TF. Each downstream gene responds to TF levels in a different way, depending on the details of the promoter. A gene regulatory function is a compact mathematical way to represent the response of each gene to different TF concentrations [1]. These responses are typically hyperbolic or sigmoidal and can be described by a Hill-like function: $\sim k\frac{[TF]^n}{[TF]^n + K^n}$, where k corresponds to the strength of the promoter, K is the affinity of TF–promoter binding, and the Hill coefficient n captures the degree of cooperativity in TF–promoter binding. Differential expression is then due to the various affinities of each promoter within the single input module.

By encoding signal information within TF concentrations and response information within promoters, cells are capable of executing regulatory programs that coordinate the timing of expression of hundreds of genes. For example, if the TF within a single input module is autoregulated by itself or its targets, the external signal triggers a slow rise of the TF, which turns on high-affinity (low K) genes early and low-affinity (high K) genes late. Some examples of this strategy include precise timing in developmental systems [2], flagellar biosynthesis in *Escherichia coli* [3], and host and viral gene expression post-infection [4].

However, what if the goal is to double the expression of all downstream genes in response to a change in an external signal?

Simply doubling the TF concentration would not work because the gene regulatory function of each promoter is not necessarily a linear function of the [TF] (unless all downstream genes have identical gene regulatory functions or identical Hill coefficients and K >> [TF], although neither case is likely) (Figure 1A). In a recent study, Cai *et al.* [5] now demonstrate how a single input module is implemented such that downstream genes respond to an external signal in a proportional manner [5]. The key idea is to encode the external signal into the length of time that promoters are exposed to the TF; this can be accomplished by controlling the frequency of promoter exposure to the TF. Then, if the TF is present half of the time, the time-averaged expression output for every gene will be half of what it would be if the TF were present all the time (Figure 1B). In some sense, rather than changing the TF concentration, the external signal changes the effective k, and every gene's expression output depends linearly on k. We refer to this mechanism as frequency-modulated (FM) coordination, after the authors.

In budding yeast, environmental stresses such as high pH and increased exposure to various ions (Mn^{2+}, Na^{+}/Li^{+}, Ca^{2+}) cause the cytoplasmic [Ca^{2+}] to rise through an as yet unclear mechanism [6]. As a result, the heterodimeric yeast calcineurin protein phosphatase is activated, leading to rapid nuclear localization of the calcineurin-responsive zinc finger transcription factor Crz1p, and the regulation of around 160 genes [7]. In previous studies, the localization of a Crz1–GFP fusion protein had been monitored in response to stress at the single-cell level at static time points and found to be heterogeneous across the population [8]. In their study, Cai *et al.* [5] monitored the dynamics of the nuclear localization of a Crz1–GFP fusion protein in single cells upon changes in external signal, in this case the extracellular [Ca^{2+}]. In a fraction of cells, Crz1–GFP immediately and synchronously relocated to the nucleus upon the step change in signal. This relocation was 'all-or-none': stronger signals resulted in nuclear localization in a larger fraction of cells but intermediate localization was never observed.

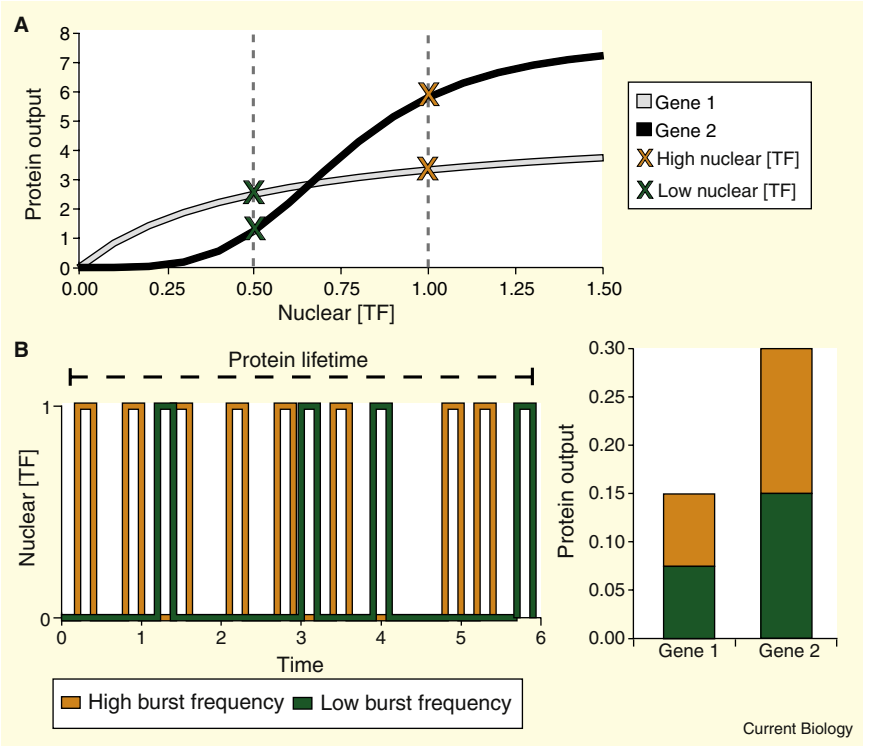

Figure 1. Achieving a proportional response with FM coordination.

(A) The gene regulatory functions of two different genes that respond to the same TF. If an external signal doubles the nuclear [TF], there is not a proportional increase in the expression of each gene. (B) FM coordination. Each square pulse represents a burst of TF localizing to the nucleus. The external signal modulates the frequency of these bursts, thereby increasing the expression in a linearly proportional manner. Although in the figure each burst has the same height and width, FM coordination holds for a distribution of burst heights and widths provided the distribution is independent of the external signal.

Even more surprising were the longer-term dynamics. Shortly after the initial localization event, Crz1–GFP returned to the cytosol. Then, Crz1–GFP localized to the nucleus for short (~2 minutes) unsynchronized bursts of time that were sustained throughout 10 hours of observation. An increase in the external signal increased the frequency of these bursts, but not their duration. By analyzing the burst statistics, two types of burst could be identified: single bursts that rapidly decayed in ~60 seconds and occurred at lower extracellular [Ca^{2+}]; and clusters of bursts lasting ~720 seconds that appeared at higher extracellular [Ca^{2+}]. Notably, the statistics of each type of burst were consistent with it being due to a single, stochastic rate-limiting step.

The fact that extracellular [Ca^{2+}] regulates the frequency of localization bursts in yeast was surprising. At least two other factors known to be regulated at the level of nuclear localization; — the phosphate-sensitive TF Pho4p and the osmosensing MAP kinase Hog1p — respond to external signals by increasing their extent of nuclear localization in a graded fashion [9,10]. However, bursts of TF localization may be more widespread than previously appreciated as two additional *Saccharomyces cerevisiae* TFs — the general stress-responsive TF Msn2p and the glucose-responsive transcriptional repressor Mig1p — also displayed localization bursts [5].

TF localization bursts immediately suggested a functional role of FM coordination in the Crz1p single input module. On average, downstream promoters 'see' Crz1p for a length of time that is proportional to the burst frequency. If the level of nuclear Crz1p (the burst height) is identical, then each promoter will express message at a rate (determined by the burst height) that is proportional to the amount of time it 'sees' Crz1p. In fact, all burst heights do not have

to be identical. FM coordination occurs as long as the distribution of burst heights is independent of extracellular [Ca^{2+}].

To test the FM-coordination hypothesis, the response of three different synthetic promoters carrying one, two or four Crz1p-binding sites was measured. Strikingly, across the range of extracellular [Ca^{2+}] tested, expression from all three synthetic promoters increased in a proportional manner. In addition, the authors ruled out the possibility that the gene regulatory function for the three synthetic promoters was identical (or similarly dependent on [Crz1p], i.e. [Crz1p] << *K* and *n* is the same for all promoters) by measuring the response of the promoters to increased Crz1p levels. To establish that FM coordination is utilized within the natural module, the response of 40 Crz1p-dependent promoters present in the genome was measured: 34 of these were found to be regulated proportionally.

One drawback to this scheme is that bursts of TF localization drive bursts of gene expression, resulting in irregular expression. Yet eukaryotic gene expression is hardly a regular process and occurs in bursts even in the presence of fixed levels of TF [11]. These high-frequency fluctuations are attenuated at the level of proteins, since most proteins are long-lived and therefore time-average these fluctuations over their lifetime. In other words, transcription and translation act as a low-pass filter, smoothing out the high-frequency fluctuations in gene activation, including those due to the bursts of TF localization.

Bursts of TF localization have gross similarities to excitatory dynamical systems — marginally stable systems where a strong fluctuation results in a long transient response. Here, cytosolic TF localization represents the marginally stable state, and localization bursts are the long transient response. A combination of positive and negative feedback loops can lead to these dynamics. The positive feedback loop is triggered by a fluctuation, resulting in a fast rise in some species. The fast rise is counteracted by a slower negative feedback loop that returns the system to the (marginally) stable state. For certain interaction strengths, the stable state is destabilized, and then this system oscillates [12]. The basic mechanism is employed in slow transcriptional feedback systems, as in *Bacillus subtilis* competence [13] and the cell cycle [14], and at faster timescales with protein–protein and protein–metabolite feedback, as in neurons [15] and the cyanobacterial circadian clock [16].

What is the biochemical mechanism responsible for the bursts of Crz1p relocalization? The feedback loops that are the source of the excitatory pulses could occur anywhere upstream of Crz1p in the Ca^{2+} signaling pathway and must involve faster protein–protein interactions. Because cytoplasmic Ca^{2+} levels are known to pulse as a result of multiple feedbacks in many different cell types [17], they represent an obvious source. Indeed, short-lived intracellular Ca^{2+} spikes were observed in yeast by fluorescence resonance energy transfer (FRET), but these only weakly correlated with Crz1p localization events. The cell cycle was also ruled out as a source of oscillations. The exact feedback loops remain to be discovered, but a clue may lie in the discovery that increasing the affinity of the calcineurin–Crz1p interaction increases the probability that a fluctuation triggers the positive feedback loop that leads to rapid dephosphorylation and localization of Crz1p.

By following molecular events in single cells in real time, Cai *et al.* [5] have demonstrated rapid TF localization bursts and connected them to FM coordination. In mammalian cells, oscillations in nucleocytoplasmic shuttling factors, such as NFκB, have been observed, but the slower, transcriptional feedback loops that drive these oscillations suggest a different functional role [18]. Therefore, bursts of TF localization could have multiple functional roles, with FM coordination being only one. In addition, FM coordination need not be implemented by bursts of TF localization: any rapid post-translational mechanism affecting TF activity should suffice. For example, the mammalian p53 protein responds to DNA damage in a pulsatile manner at the level of concentration, but the p53 pulses are slow and target genes are expressed in a pulsatile manner [19], rather than being time-averaged.

How large a role does FM coordination play in biology? It should be straightforward to test for the presence of FM coordination in many single input modules by looking for the signature proportional response of target genes to the appropriate external signal. A more difficult task will be to monitor post-translational changes of proteins in real-time at the single-cell level to understand the mechanism that produces the necessary bursts in TF activity. In addition, the physiological role for FM coordination in Crz1p-dependent gene expression remains to be defined. One obvious possibility is that target genes express proteins that interact in a manner in which stoichiometry must be preserved. Identifying a collection of FM-coordinating systems should shed light on the physiological role and prevalence of FM coordination in biology.

References

1. Alon, U. (2006). An Introduction to Systems Biology: Design Principles of Biological Circuits (Boca Raton, FL: CRC Press).
2. Freeman, M. (2000). Feedback control of intercellular signalling in development. Nature *408*, 313–319.
3. Kalir, S., McClure, J., Pabbaraju, K., Southward, C., Ronen, M., Leibler, S., Surette, M.G., and Alon, U. (2001). Ordering genes in a flagella pathway by analysis of expression kinetics from living bacteria. Science *292*, 2080–2083.
4. Ball, L.A. (2007). Virus replication strategies. In Fields Virology, B.N. Fields and D.M. Knipe, eds. (Philadelphia, PA: Lippincott, Williams, and Wilkins), pp. 119–140.
5. Cai, L., Dalal, C.K., and Elowitz, M.B. (2008). Frequency-modulated nuclear localization bursts coordinate gene regulation. Nature *455*, 485–490.
6. Cyert, M.S. (2003). Calcineurin signaling in Saccharomyces cerevisiae: how yeast go crazy in response to stress. Biochem. Biophys. Res. Comm. *311*, 1143–1150.
7. Yoshimoto, H., Saltsman, K., Gasch, A.P., Li, H.X., Ogawa, N., Botstein, D., Brown, P.O., and Cyert, M.S. (2002). Genome-wide analysis of gene expression regulated by the calcineurin/Crz1p signaling pathway in Saccharomyces cerevisiae. J. Biol. Chem. *277*, 31079–31088.
8. Stathopoulos-Gerontides, A., Guo, J.J., and Cyert, M.S. (1999). Yeast calcineurin regulates nuclear localization of the Crz1p transcription factor through dephosphorylation. Genes Dev. *13*, 798–803.
9. Mettetal, J.T., Muzzey, D., Gomez-Uribe, C., and van Oudenaarden, A. (2008). The frequency dependence of osmo-adaptation in Saccharomyces cerevisiae. Science *319*, 482–484.
10. Springer, M., Wykoff, D.D., Miller, N., and O'Shea, E.K. (2003). Partially phosphorylated Pho4 activates transcription of a subset of phosphate-responsive genes. PLoS Biol. *1*, E28.
11. Maheshri, N., and O'Shea, E.K. (2007). Living with noisy genes: how cells function reliably with inherent variability in gene expression. Annu. Rev. Biophys. Biomol. Struct. *36*, 413–434.

12. Barkai, N., and Leibler, S. (2000). Circadian clocks limited by noise. Nature *403*, 267–268.
13. Suel, G.M., Garcia-Ojalvo, J., Liberman, L.M., and Elowitz, M.B. (2006). An excitable gene regulatory circuit induces transient cellular differentiation. Nature *440*, 545–550.
14. Pomerening, J.R., Kim, S.Y., Ferrell, J., and James, E. (2005). Systems-level dissection of the cell-cycle oscillator: Bypassing positive feedback produces damped oscillations. Cell *122*, 565–578.
15. Hodgkin, A.L., and Huxley, A.F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. *117*, 500–544.
16. Rust, M.J., Markson, J.S., Lane, W.S., Fisher, D.S., and O'Shea, E.K. (2007). Ordered phosphorylation governs oscillation of a three-protein circadian clock. Science *318*, 809–812.
17. Berridge, M.J., Bootman, M.D., and Roderick, H.L. (2003). Calcium signalling: dynamics, homeostasis and remodelling. Nat. Rev. Mol. Cell Biol. *4*, 517–529.
18. Nelson, D.E., Ihekwaba, A.E., Elliott, M., Johnson, J.R., Gibney, C.A., Foreman, B.E., Nelson, G., See, V., Horton, C.A., Spiller, D.G., *et al.* (2004). Oscillations in NF-kappaB signaling control the dynamics of gene expression. Science *306*, 704–708.
19. Batchelor, E., Mock, C.S., Bhan, I., Loewer, A., and Lahav, G. (2008). Recurrent initiation: A mechanism for triggering p53 pulses in response to DNA damage. Mol. Cell *30*, 277–289.

Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.
E-mail: narendra@mit.edu

DOI: 10.1016/j.cub.2008.10.032

Group Decisions: How (Not) to Choose a Restaurant with Friends

Subordinate baboons voluntarily follow the dominant group member to foraging patches where they themselves starve. One-sided preservation of social ties seems to prevail over fair decision sharing, contradicting recent theory.

Larissa Conradt

As humans, we are used to making decisions not as individuals acting alone, but collectively and interactively, as a group. It is obvious that our sophisticated societies could not persist without collective decision making, whether this be choosing a restaurant with a group of friends, electing a political leader, or deciding on international actions to tackle climate change or financial meltdown. Because our ability to make decisions collectively dictates not only the nature and quality of specific decision outcomes, but also the stability of society itself, it is not surprising that collective decision making has been a central topic of philosophy and the social sciences for millennia (for example, see Plato's *The Republic* written in 360 BC).

What might be less obvious is that collective decisions are just as important for other social animals as they are for humans. Dispersing swarms of bees and ants collectively choose new nest sites on which depend their survival and future reproduction. Homing and migrating birds collectively decide on communal routes that affect their chances of arriving successfully. Bats collectively select roosting sites that are crucial for survival and breeding. Swarms of insects, shoals of fish, flocks of birds, groups of carnivores, herds of ungulates and troops of primates collectively decide on the direction of group movements and the timing of group activities, with important fitness consequences to all group members. Cooperative species, such as eusocial insects and communal breeders, collectively decide job allocation in crucial communal enterprises, such as supplying food to the hive, rearing young, defending the group against predators, and hunting prey. There are many more examples.

While the study of collective decision-making in social animals is still relatively young, it is now expanding rapidly [1] and has been a central theme at several recent international conferences. However, with perhaps the exception of empirical studies on insects [2–5], theoretical developments [6–10] have, so far, advanced far ahead of empirical evidence. The recent *Current Biology* paper by King *et al.* [11] is a welcome step towards closing this gap. The study is remarkable in three respects. Firstly, the work was done on wild primates (Figure 1), rather than on captive or semi-free ranging ones. Secondly, the work is experimental, rather than merely observational, in character. Thirdly, and most importantly, the study measures one of the main factors considered crucial in collective decision making from a theoretical point of view, namely, the 'consensus costs'. These are the costs, to individual group members, of reaching a consensus [1,8]. To the best of my knowledge, this is a first.

King *et al.* [11] presented two wild baboon groups with experimental food patches within their home ranges, additionally to natural patches. In experimental patches, food intake amongst group members was highly skewed in such a way that a minority of (dominant) group members had a very high food intake, while the remaining majority of (subordinate) group members had hardly any food intake at all. In contrast, in natural patches, food intake was relatively evenly spread across group members. Thus, if the group chose an experimental over a natural foraging patch, the majority of group members would incur substantial consensus costs in terms of reduced food intake. On the other hand, if the group chose a natural over an experimental patch, a minority of dominant members would incur consensus costs. Theory predicts that, under such circumstances, groups should move to the patch that benefits the majority of group members, and, thus, minimises overall consensus costs [6–9]. That is, the group should choose a natural patch. What King *et al.* [11] observed was exactly the opposite. Both baboon groups consistently visited experimental patches in preference to natural patches. Coercion by dominant individuals did not play a role in this choice.